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USSR VACCINES AGAINST POLYSEASONAL NEUROINFECTIONS

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Neuroinfections which afflict human beings comprise approximately one third of all organic diseases of the nervous system. Among these infections a special place is occupied by the so-called endemic polyseasonal neuroinfections, which are characterized by specific clinical syndromes.

As their name indicates, polyseasonal neuroinfections occur everywhere at all seasons. However, there is occasionally a rise of the incidence of such diseases in the winter and in the spring.

Notwithstanding the fact that these infections are encountered considerably more often than epidemic diseases, investigation of their etiology is still carried out on an inadequate scale and is connected with some difficulties. The individual nosological forms of the diseases of this type are not sharply differentiated. The study of these diseases is also made difficult by the occurrence of a great number of chronic and recurrent forms and by the absence of clear epidemiological data.

Some of the best investigated polyseasonal neuroinfections are poliomyelitis, lymphocytic choriomeningitis, acute encephalomyelitis, and multiple sclerosis. The two last-mentioned diseases are etiologically interrelated and have similar clinical and pathomorphological manifestations. Their basic characteristic is occurrence of a multiple focal demyelinization. This was noted by clinicists long ago. However, a study of the problem under experimental conditions became possible only after M. S. Margulis, V. D. Solov'yev, and A. K. Shubladze succeeded in 1942 in isolating for the first time the virus of acute human encephalomyelitis.

The laboratory diagnosis of virus infections is based on the isolation of the virus from patients and proof of the presence of specific antibodies by means of serological reactions (neutralization of the virus and complement fixation). The isolation of the virus succeeds best in the acute stage, i. e., during the first 5-10 days of the disease.

Persons convalescing from acute encephalomyelitis have in their body antibodies which neutralize the virus. The same antibodies were found in the blood of persons suffering from multiple sclerosis. Thus serological investigations furnished a decisive argument in favor of the etiological identity of acute encephalomyelitis with multiple sclerosis. We are inclined to think that whenever the presence of multiple sclerosis is established by serological tests one must assume that it has been induced by the virus of acute encephalomyelitis.

The causative factor of acute encephalomyelitis and of multiple sclerosis has been subjected to an intensive study for 13 years. Methods of specific diagnosis and therapy are being developed. It has been established that the virus can be cultured on chicken embryos and on malignant tumors of mice. White mice, rats, guinea pigs, rabbits, dogs, simians, and some species of birds are susceptible to the virus. In all of these animals the virus brings about an acute and lethal infection. Chicks and young adult chickens, in addition to developing an acute infection, can be used to reproduce the chronic form of the disease which persists for 1-2 years and exhibits periods of remission and aggravation.

The existence of a close antigenic connection between the virus of acute encephalomyelitis and the virus of rabies has been established. In other words, in addition to the group which is antigenically related to the virus of spring-summer tick encephalitis and which comprises the viruses of Scotch encephalitis, two-wave milk fever, and Omsk hemorrhagic fever, there is another group to which the viruses of rabies, acute human encephalomyelitis, acute encephalomyelitis of foxes, and some forms of equine encephalomyelitis belong.

The discovery of the causative factor of acute human encephalomyelitis and of its connection with multiple sclerosis made it possible to develop methods of specific diagnosis and therapy of these diseases.

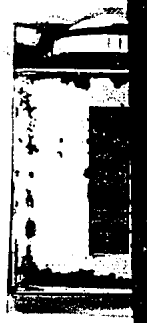
In 1945, M. S. Margulis and V. D. Solov'yev, together with the authors of this article, used for the therapy of patients suffering from acute encephalomyelitis and multiple sclerosis a vaccine prepared from virus of acute encephalomyelitis that had been killed with formalin. It was established that therapy with the vaccine prepared in this manner brings about recovery or a considerable improvement in 30% of the cases and that this therapy results in stabilization of the pathogenic process in another 30% of the cases. Therapy with the vaccine was unsuccessful in some cases. The fact that the vaccine was not very effective in individual cases has been ascribed to the fact that the diagnosis of the disease was not sufficiently accurate. It is known that in a number of cases a timely and correct diagnosis of multiple sclerosis is rather difficult, because the appearance of general symptoms accompanied by an affliction of the nervous system can be brought about by tumors or various types of infectious encephalitides, so that an incorrect conclusion is possible as far as application of therapeutic measures is concerned. At present, production of the vaccine against acute encephalomyelitis and multiple sclerosis has been organized at the Khar'kov Institute of Sera and Vaccines imeni I. I. Mechnikov. The preparation which is being supplied should be administered subcutaneously. A course of treatment consists of no less than 10-12 injections of 3-5 milliliters each. The patient should be subjected to two or three courses of treatment with the vaccine during a year.

The therapy can be carried out not only under clinical but also under ambulatory conditions, under the observation of a neuropathologist. In the latter case the vaccine is obtained from the Main Pharmacy Administration and is stored at a temperature of +2-10°. The vaccine preserves its effectiveness for one year beginning with the time of preparation.

The patients do not always stand a number of subcutaneous injections well.

A. G. Panov and S. Ya Gaydamovich proposed an intracutaneous method of vaccine therapy in which small doses are frequently administered. Clinical tests have shown that the effectiveness of this method is even somewhat higher than that of the method of subcutaneous administration. Furthermore, application of the vaccine by this method reduces the cost of the treatment. Beginning with 1955, the Khar'kov Institute of Sera and Vaccines supplies the vaccine not only in large packages but also in small packages containing quantities appropriate for the intracutaneous method of therapy. In this method of treatment 0.2 milliliters of vaccine are injected into the skin of the forearm. The number of injections is 7-10 per course of treatment.

The intracutaneous administration of the vaccine is accompanied by a specific skin reaction. The stronger the reaction of the patient to an intracutaneous injection of the vaccine, the greater the expectation that the specific treatment will be effective. Starting from this premise, the diagnostic value of the skin test in acute encephalomyelitis and multiple sclerosis was investigated.



The serological method of the specific diagnosis of these two diseases yields positive results in approximately 40-50% of the cases.

Intracutaneous tests are used for the diagnosis of infectious diseases, primarily chronic diseases in the course of which there is sensitization of the organism towards the infectious agent in question. Skin tests have been applied widely in the diagnosis of tuberculosis, tularemia, and brucellosis. As far as human virus infections are concerned, the skin test has been proposed for use in venereal lymphogronuloma, herpes, psittacosis, and epidemic parotitis. The diagnostic value of the skin test in epidemic hepatatis is being subjected to study.

With a view of carrying out diagnosis by means of skin tests in multiple sclerosis, different methods of preparing the diagnostic antigen were investigated. The inactivation of the virus for the preparation of the diagnostic antigen was carried out by heating, treatment with formalin, and treatment with ultraviolet light. Both purified and concentrated antigens were used for this purpose. However, clinical investigations have shown that the ordinary forminalinized vaccine is a good antigen for the skin test. The period during which a diagnostic vaccine of this type is effective does not exceed 4 months beginning with the time of preparation. The skin test is carried out as follows: 0.2 milliliters of the vaccine are introduced intracutaneously into the inner surface of the forearm, while the normal antigen used for control is injected into the other arm.

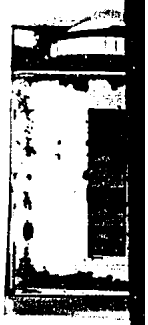
The control vaccine does not contain the virus of acute encephalomyelitis. Twenty-four to 40 hours after introduction of the effective vaccine, reddening and infiltration of varying intensity appear at the site of introduction of the active vaccine. The reaction tapers off after 3 or 4 days. An infiltrate covering an area of 2 x 3 centimeters (6 square centimeters) or larger must be regarded as a positive reaction. The infiltrate which develops at the site where the control antigen has been injected does not exceed one square centimeter as a rule.

The results obtained in investigations of the method of skin tests carried out at two clinics distant from each other coincided on the whole. According to data obtained by L. P. Popova, positive results in multiple sclerosis were observed in 98.5% of the patients. According to data reported by G. S. Kolesnikov, positive results were obtained in 93.5% of the cases. Among those suffering from other diseases of the nervous system, the tests yielded a doubtful result in 2.03% of tne cases and a positive result in only 1.01% of the cases.

The high percentage of positive specific reactions obtained in acute encephalomyelitis and multiple sclerosis makes it possible to use these reactions for diagnostic purposes in practical clinical work. The instruction on the use of the skin test in these diseases has been confirmed by the Ministry of Health USSR. The Khar'kov Institute of Sera and Vaccines has undertaken the production of the antigen.

During the 10 years which have passed since the time when the vaccine was proposed for the therapy of multiple sclerosis and of acute encephalomyelitis, a large volume of published data has been accumulated. These data confirm the effectiveness of the method.

The total number of patients under observation who have been subjected to vaccine therapy comprises more than 500. This figure is considerably lower than the total number of patients who have been treated by this method under stationary and ambulatory conditions since the development of the vaccine. The indexes of effectiveness, according to the data published by different authors, vary between 30-60%. During the first years when observations were carried out these indexes were higher. This is explained by the fact that immediately after treatment improvement takes place in almost all cases. However, the lasting



nature of this improvement can be established only on the basis of catamnestic observations. It has been already pointed out by M. S. Margulis that in estimating the effectiveness of the therapy, one must primarily take into consideration whether or not a significant improvement has taken place. Under significant improvement one understands a reduction or disappearance of motor, sensory, and vegetative disturbances accompanied by an improvement in the sense of well-being. This state of significant improvement has been achieved in 30% of the cases when vaccine therapy of acute encephalomyelitis and multiple sclerosis was applied. Furthermore, the success attained in scientific research contributes to the assurance that specific therapy with preparations derived from the virus of acute encephalomyelitis will be further improved from every standpoint. It is highly probable that purified and concentrated vaccines, when they become available, will be more effective.

Supplementary therapy with a specific immune serum or with gamma globulin derived from the immune serum will make it possible to obtain still better results. Research along these lines has been undertaken by a group working at the Virus Division of the Khar'kov Institute of Sera and Vaccines.

It is important to note that as far as many virus infections are concerned, virologists have proposed and developed methods of specific diagnosis, prophylaxis, and therapy. However, the production of antivirus preparations develops very slowly and the agents that have been developed are not widely enough advertised and introduced into practical public health work rapidly enough. For instance, practicing physicians do not have enough information on the instructions issued by the Ministry of Health USSR in regard to the diagnosis and prophylaxis of spring-summer tick encephalitis. This also applies to the instructions on the control of poliomyelitis and epidemic hepatitis; on the diagnosis and prophylaxis of epidemic influenza, paratitis, and ornithoses; on the prophylaxis of measles; on the control of sand-fly fever and hemorrhagic fevers; and on the diagnosis and therapy of acute encephalomyelitis and multiple sclerosis.

The exact adherence to instructions is often made difficult by reason of the fact that standard antivirus diagnostic preparations are not available. If such preparations were at the disposal of clinical laboratories, these laboratories could carry out a much greater number of analyses of value in the diagnosis of complex forms of infections.

In addition to providing diagnostic antigens, it is of importance that the matter of supplying standard diagnostic and therapeutic sera be organized properly. It is of particular importance to improve serum preparations and to organize the production of gamma globulin derived from immune sera. So far this undertaking has been successfully begun only by the personnel of the Moscow Institute of Vaccines and Sera imeni I. I. Mechnikov.

The new, improved antivirus vaccines are also being introduced into practical work rather slowly. This refers to the dry brain and egg vaccines against spring-summer encephalitis, the egg vaccine against smallpox, and the brain vaccine against acute encephalomyelitis and multiple sclerosis (for subcutaneous administration). The achievements of science in this field must become available to practicing physicians.

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